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A Case of Albright's Hereditary Osteodystrophy-Like Syndrome Complicated by Several Endocrinopathies: Normal Gsα Gene and Chromosome 2q37*

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ABSTRACT

We report a sporadic case of Albright's hereditary osteodystrophy (AHO)-like syndrome with several endocrinopathies. A 37-yr-old woman had an appearance of AHO but did not have renal PTH resistance. Her case was complicated by non-insulin-dependent diabetes mellitus with severe insulin resistance, central diabetes insipidus, and hyposecretion of GH. Most patients with AHO are found in a family of pseudohypoparathyroidism type-Ia and have a heterozygous mutation that inactivates the α-subunit of Gs (Gsα), the stimulatory regulator of adenylyl cyclase. Some sporadic cases occur in which patients with phenotype similar to AHO have a deletion of chromosome 2q37. However, in this patient, both the Gsα gene structure and the biological activity were normal. In addition, chromosome analysis revealed a normal pattern with no visible deletion of chromosome 2q37. Our findings suggest that one or more other factors may be involved in the pathogenesis of AHO-related disease. (*J Clin Endocrinol Metab* **83:** 1563–1565, 1998)

ALBRIGHT'S hereditary osteodystrophy (AHO) is a congenital genetic syndrome characterized by short stature, obesity, round face, mental weakness, and sc calcifications and/or brachymetaphalangism (1). Many patients with AHO inherit reduced biological activity of Gsα, the α subunit of Gs, the stimulatory regulator of adenylyl cyclase. A number of Gsα mutations were found in AHO patients (2–9). AHO is usually associated with resistance to PTH and some other hormones whose receptors are coupled to Gs [pseudohypoparathyroidism type-Ia (PHP-Ia)]. The AHO phenotype alone that appears in a family of PHP-Ia is termed pseudopseudohypoparathyroidism.

Some sporadic cases occur in which patients with AHO-like phenotype have a small terminal deletion of chromosome 2 [Del(2)q37] (10, 11). These patients do have brachydactyly and mental retardation but lack renal PTH resistance and sc calcification.

Here, we report a sporadic case of AHO-like syndrome complicated by several hormonal disorders.

Subjects and Methods

Profile of the patient

The patient is a 37-yr-old woman who is short (height 147 cm) and obese (wt, 68 kg) and has a round face, a short neck, marked shortening of both fifth metacarpals (Fig. 1), and mental retardation. However, she has no evidence of ectopic sc calcification. She presented as normocalcemic; and her serum levels of intact PTH, urinary cAMP excretion, and tubular reabsorption of phosphate all were within the normal range. She had no PTH resistance in the kidney, as indicated by the Ellsworth-Howard test (Table 1B).

Her case was complicated by non-insulin-dependent diabetes mellitus. Her 24-hr urine CPR was normal, and her plasma insulin was hyperresponsiveness to iv injection of glucagon or arginine, indicating that her insulin secretory capacity was well conserved (Table 1). Her glucose disposal rate, by the hyperinsulinemic-euglycemic glucose clamp test, was low, indicating that she had severe insulin resistance. Her metabolic control for diabetes improved with diet therapy.

Her case was further complicated by central diabetes insipidus (DI). She had poly- and hyposthenuria. Her plasma osmolality was slightly high; nevertheless, her serum arginine-vasopressin level was low. A hypertonic saline stimulating test showed central DI pattern. Moreover, the signal intensity on T1-weighted magnetic resonance imaging of neurohypophyshysis was not detected.

In addition, several other hormonal abnormalities were present (Table 1). Her plasma GH and somatomedin C were low. Her plasma GH responses to both GHRH and arginine were low. Her basal plasma glucagon, ACTH, and cortisol levels were slightly higher than normal; but from other clinical examinations, it is unlikely that she had a glucagonoma or Cushing's disease/syndrome. She did not have a pituitary adenoma. Her thyroid and gonadal functions were normal. She had first menstruation at the age of 13, and thereafter she had irregular menses and was sterile. Computed tomography scanning and ultrasonographic study revealed no evidence of the organized disease in her uterus and ovaries, but she neglected to undergo the other gynecological check-ups.

Her parents and siblings were normal in height and weight and did not have AHO or any hormonal disorders.

Methods

To try to diagnose and identify the pathogenesis, we checked the genetic defects associated with the two likely diseases. Specifically, to check AHO, we looked for a mutation and low activity of Gsα. To check AHO-like phenotype, we looked for deletion of chromosome 2q37.

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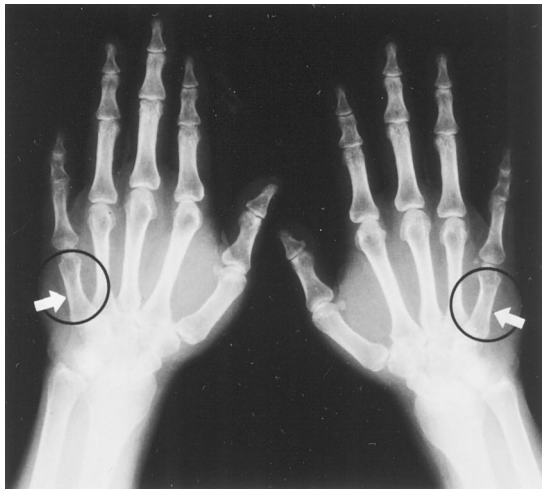


FIG. 1. Plain radiograph of hands, illustrating the shortening of bilateral fifth metacarpals.

Sequencing determination of Gsα

Genomic DNA was extracted from peripheral leukocytes by the standard method (12). The Gsα mutations were identified both by a solid-phase PCR-direct sequence method and by the sequencing of the amplified DNA fragments subcloned into the plasmid. To amplify exon 2–13, including each bordering intron region of Gsα gene, the primers described previously (13) were used. For the PCR to amplify exon 1, two primers were used (5′-ATGGGCTGCCTCGGGAACAG-3′, and 5′-TTACCCAGCAGCAGCAGGCG-3′).

Measurement of the biological activity of Gsα

The biological activity of Gsα was determined with a complementation assay based on the ability of solubilized extracts of erythrocyte membranes prepared from S49 cyc(−) murine lymphoma cells, which genetically lack Gsα protein (14). As the control for this assay, blood cells extracted from three healthy normal subjects were used.

Analysis of chromosomal and microsatellite marker within 2q37

Chromosomal analysis on peripheral lymphocytes was performed by the standard method, in Shionogi Biomedical Laboratory (Osaka, Japan). Typing of three polymorphic markers (D2S395, D2S140, and D2S125) (15), located within the important regions of chromosome 2q37, were also analyzed for this patient and her parents (10).

Results

We did not find any mutations in exon 2–13 or in the bordering intron regions of the Gsα gene in this patient. For exon 1, we also did not find any mutations in the DNA fragment from 20 bp downstream of the initiation codon to the region of the donor site of intron 1. We were not able to perform PCR for the other DNA fragment of exon 1, possibly because guanine and cytosine were rich in these bordering regions.

The Gsα bioactivity of this patient was normal. [103 ± 19% (n = 3) of the average of the three normal subjects]

The chromosomes of the patient were 46, XX normal female karyotype, with no visible deletion on 2q on metaphase spreads (Fig. 2). Her alleles were all heterogeneous, one from her mother and other from her father.

Discussion

We have shown a case of AHO-like syndrome complicated by several endocrinopathies. The patient has obesity, brachydactyly, and mental retardation, which is typical in AHO patients with Gsα deficiency. However, the patient does not have PTH resistance, sc calcification, or any family history that is especially consistent with AHO-like phenotype. A definite diagnosis is not possible because the genetic defects causing AHO or AHO-like phenotype are

TABLE 1A. Blood chemical and hormonal analysis and endocrine function tests

		Data	(Normal value)
Serum	Calcium	2.4 mmol/L	(2.2–2.8)
	Phosphate	1.18 mmol/L	(0.95–1.35)
Plasma	PTH-C	0.3 ng/mL	(<1.2)
	Intact PTH	39 pg/mL	(10–50)
Urinary cAMP excretion		3.0 nmol/dl GF	(2.5–5.0)
Plasma	Insulin (IRI)	136.8 pmol/L	(<120)
	C-peptide (CPR)	1.5 nmol/L	(0.33–1.2)
24-h urine	CPR	16.6 μmol/day	(5.3–39.7)
Plasma	Osmolality	295 mosmol/L	(275–290)
	Arginine-vasopressin	0.2 ng/L	(0.8–6.3)
Plasma	ACTH	78 pg/mL	(6–55)
	Cortisol	17.68 μg/dL	(5–15)
Urine	17-OHCS	10.7 mg/day	(1.9–6.1)
	17-KS	4.4 mg/day	(3.1–8.8)
Plasma	GH	1.7 μg/L	(<5)
	Somatomedin-C	0.2 U/mL	(0.46–1.68)
	Free T_3	3.3 pg/mL	(3.24–5.44)
	Free T_4	1.0 ng/dL	(1.28–2.08)
	TSH	2.97 μU/mL	(0–5)
	LH	4.1 IU/L	(1.6–9.5)
	FSH	12.0 IU/L	(1.9–9.5)
	Estriol	130 pg/mL	(23–145)
	Estradiol	<5 μg/L	(<5)
	Prolactin	7.4 μg/L	(2.7–8.1)
	Glucagon	280 ng/L	(40–180)

TABLE 1B. Ellsworth-Howard test

Inject 100 U of PTH	120 min before	60 min before	60 min later	120 min later
iP in urine (mg)	19	22	26	35
cAMP in urine (μmol)		10	more than 300	

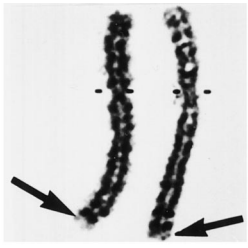
TABLE 1C. Glucagon stimulating test

	(min)	0	5	30
Plasma glucose	(mg/dL)	216	229	236
IRI	(mU/L)	22.8	247.7	
CPR	(ng/mL)	3.7	13.8	

TABLE 1D. Stimulating test for GH secretion

(min)	0	30	60	90	120
Plasma GH (μg/L) by 100 μg GRH stimulation	1.4	2.6	3.6	6.0	3.4
Plasma GH (μg/L) by 30 g Arginine stimulation	1.7	0.4	1.9	5.7	2.6

1 mg Dexamethasone depression test (one dose method): Plasma cortisol on the next morning (4.8 μg/dL). Hyperinsulinemic-euglycemic glucose clamp test: Glucose disposal rate, lower than 1.0 mg/kg·min (Normal range: 6.0–10.0).



	D2S395	D2S140	D2S125
Patient	(144 / 146)	(151 / 153)	(88 / 100)
Mother	(146 / 146)	(151 / 151)	(88 / 100)
Father	(144 / 152)	(153 / 155)	(88 / 92)

FIG. 2. Ideogram of chromosome 2 and analysis of microsatellite markers near the 2q37 locus. *Upper*, Ideogram of chromosome 2, with no deletion of 2q37; *lower*, analysis of microsatellite markers near the 2q37 locus. The values *in parentheses* indicate the base pair sizes of DNA that were amplified by using primer described by Gyapay *et al.* (16). The allele *enclosed with a square* was derived from the mother and the *underlined* allele was derived from the father.

not present: specifically, the patient did not have Gsα defect or Del(2)q37.

Although most patients with AHO have reduced bioactivity of Gsα, because of a gene mutation (2–9), our case seems to have normal gene structure and bioactivity of Gsα. However, it should be noted that we were unable to examine a part of exon 1 for a mutation. An instructive mutation (R231H) of the Gsα was reported (9), in which reduced bioactivity could not be detected using the erythrocyte Gs assay (qualitative defect). Thus, it is still possible that a mutation in the unexamined part of exon 1 results in a qualitative Gs defect.

It was reported that Del(2)q37 is important in the pathogenesis of AHO-like phenotype or brachydactyly (10, 11). These cases, which occur sporadically, involve subjects who have mental retardation but lack PTH resistance and sc calcification. Clinically, our patient may belong to this category. Although our patient did not have gross Del(2)q37, she may have a small rearrangement or a point mutation in the (as yet unidentified) relevant gene in this region.

The present case was complicated by several endocrinopathies: non-insulin-dependent diabetes mellitus, central DI, and GH deficiency. However, the first two seem to be unrelated to AHO or AHO-like phenotype. Insulin resistance and hyposecretion of ADH are not associated with Gs defect. Even though we did not find a Gsα defect, the third one (the GH deficiency) may be related to a Gs defect, because the GHRH receptor couples to Gs and, in fact, the conditions of some patients with PHP-Ia are complicated by GH deficiency (16). In addition, a case of AHO-like phenotype with Del(2)q37 was complicated with the low secretion of GH (10), suggesting a possible causal relation.

Thus, genetics in the pathogenesis of AHO-related diseases is still complicated. One or more other factors, in addition to the Gsα gene mutation and the rearrangement of chromosome 2q37, may be involved. Identification of the genetic defect will contribute to our understanding of the hormone action and the pathogenesis of AHO-related diseases.

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